

# The Role of Insulin-Like Growth Factors and Insulin-Like Growth Factor–Binding Proteins in the Nervous System

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**ABSTRACT:** The insulin-like growth factors (IGF-I and IGF-II) and their receptors are widely expressed in nervous tissue from early embryonic life. They also cross the blood brain barriers by active transport, and their regulation as endocrine factors therefore differs from other tissues. In brain, IGFs have paracrine and autocrine actions that are modulated by IGF-binding proteins and interact with other growth factor signalling pathways. The IGF system has roles in nervous system development and maintenance. There is substantial evidence for a specific role for this system in some neurodegenerative diseases, and neuroprotective actions make this system an attractive target for new therapeutic approaches. In developing new therapies, interaction with IGF-binding proteins and other growth factor signalling pathways should be considered. This evidence is reviewed, gaps in knowledge are highlighted, and recommendations are made for future research.

**KEYWORDS:** IGF, IGFBP, nervous system, neurodegenerative disease

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## Introduction

There is evidence that the insulin-like growth factors (IGF-I and IGF-II) have key roles in nervous system development and function. This system is phylogenetically related to insulin and its receptors, and the IGF/insulin system is evolutionarily conserved.<sup>1</sup> The IGFs cross the blood-brain barriers<sup>2</sup> and have endocrine roles in brain. They bind with high affinity to a family of IGF-binding proteins (IGFBPs) which regulate availability of IGFs to interact with their receptors.<sup>3</sup> It is well known that the action and expression of each IGFBP is cell- and tissue-specific.<sup>4</sup> Therefore, an understanding of IGFBPs in nervous tissue is essential to understanding the paracrine/autocrine roles as well as the actions of endocrine IGFs in normal physiology and diseases of the nervous system. Neurodegenerative disorders are increasing in prevalence, and a knowledge of the IGF system is likely to be important in finding therapeutic targets.

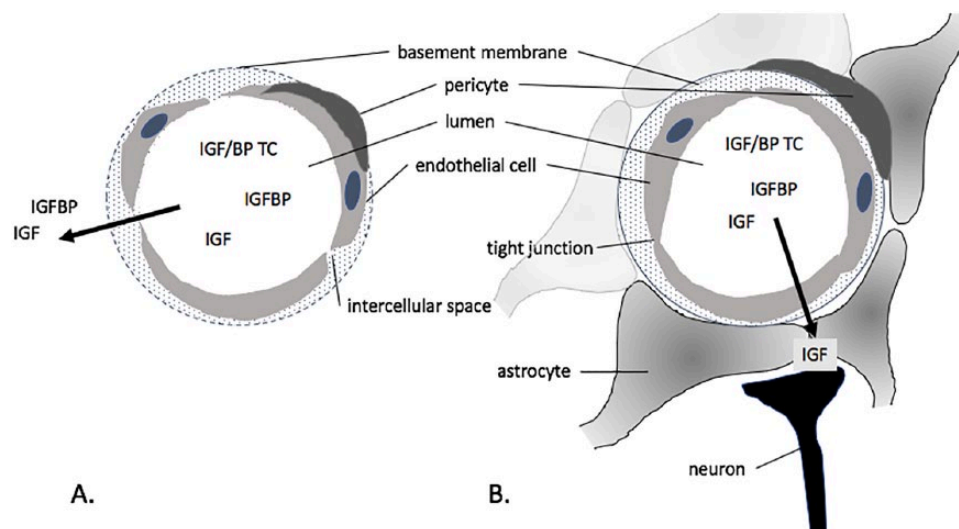
The aim of this review is to present a broad perspective of current knowledge about the role of IGFs and IGFBPs in the nervous system. Articles included were retrieved through PubMed using a combination of the MeSH search term 'Nervous System' and the search term 'IGF' in all fields. Papers published between January 2014 and September 2018 were retrieved and the abstracts scanned for relevant papers. Key contributions to the field predate 2014 and therefore, in addition, the author's own EndNote™ database of IGF papers prior to 2014 was searched using the term 'Nervous System'. References within the articles obtained by these methods were also used to retrieve key papers. The field is dominated by experimental studies in rodents and this may be a limitation in identifying relevant therapeutic targets for human disease. Where possible, publications that focus on the human IGF system are presented in this review.

An overview of the IGF system and its expression and action, with a focus on the nervous system, will first be presented. This will set the scene for a discussion of the role of the IGF system in nervous system disorders, and the potential of this system in therapeutics. Signposting to future research will be included in the concluding section.

## IGF System Overview

The IGF system has general roles in growth and metabolism, and ageing, that are evolutionarily conserved.<sup>1</sup> Insulin-like growth factor 1 and IGF-II are evolutionarily related to proinsulin and share structural similarity so that all three bind to type 1 IGF receptors (IGF1R) and insulin receptors (IR), which also share structural similarity.<sup>5</sup> There are two isoforms of IR, IRA and IRB, that can form heterodimers, and each isoform can form heterodimers with IGF1R subunits.<sup>6,7</sup> All of these receptors are activated through ligand-induced autophosphorylation and subsequent phosphorylation of other tyrosine-containing substrates and enzyme cascades, including the phosphatidylinositol-3 kinase (PI3K)–protein kinase B (Akt) pathway.<sup>8</sup> While IGFs have a higher affinity than insulin for IGF1R and are therefore likely to have important physiological roles through that pathway, the physiological roles of the IR isoforms and their hybrids are not fully established, and are likely to be influenced by differing affinities for IGF-II.<sup>6</sup> IRA homodimers and IRA/IGF1R hybrids have high affinity for IGF-II and have a role in cancer cell growth.<sup>7</sup> The IGF-II/mannose-6-phosphate receptor (IGF2R) is a structurally distinct cell-surface receptor that plays a role in internalising IGF-II and not IGF-I, as well as trafficking lysosomal enzymes.<sup>9</sup> The IGF-II binding domain of IGF2R is also present in the circulation and can block IGF-II-induced cell





**Figure 1.** IGFs and IGFBPs that are not associated in a ~140 kDa ternary complex (TC) with an acid-labile subunit readily cross the endothelium of fenestrated capillaries (A) unbound or in binary complexes. Passage across the blood-brain barrier into brain parenchyma (B) involves active transport of IGFs that are not in binary or ternary complexes.

growth.<sup>9</sup> A key characteristic of the IGFs, not shared with insulin, is a high affinity for members of a family of IGFBPs<sup>10</sup> that have distinct functional roles. They can stimulate or inhibit IGF actions and have IGF-independent effects, depending on the IGFBP, post-translational modifications and cellular milieu.<sup>11,12</sup>

Our understanding of the IGF system is founded on the original work of Salmon and Daughaday<sup>13</sup> who discovered the existence in the circulation of pituitary-dependent mediators of tissue growth. Later, this view expanded to encompass paracrine/autocrine roles.<sup>3</sup> The endocrine IGF system will be discussed first. The liver plays a central role in the production of endocrine IGFs, secreting a ternary complex of approximately 140 kDa that has a long circulating half-life (hours-days).<sup>14,15</sup> Hepatic IGF and an acid-labile subunit are produced by hepatocytes and enter the circulation in association with IGFBP-3 or IGFBP-5, produced by non-parenchymal cells. Circulating IGF-I and IGF-II are mainly associated in these ternary complexes, which have long circulating half-lives. Since IGF-I and the acid-labile subunit are both growth hormone (GH)-dependent, IGF-I is an ideal biomarker of GH, which is secreted in pulsatile bursts by the pituitary and has a short circulating half-life (minutes).<sup>16</sup> The insulin-like growth factor I is also positively regulated by total caloric and protein intake and by insulin,<sup>15</sup> so that the IGF-I in the circulation is also a marker of nutritional status. While most IGF-I and IGF-II in the circulation is associated in ternary complexes, IGF (~7 kDa) also associates in binary complexes with IGFBPs (~25–45 kDa) in the circulation and at the tissue level, and a proportion is 'free' to interact with cell surface receptors.<sup>12</sup> Thus, circulating IGFs and IGFBPs are part of a dynamic system, crossing the endothelium of fenestrated and sinusoid capillaries rapidly (minutes-hours), alone or associated in binary complexes (Figure 1A).

IGFs and IGFBPs are ubiquitously produced and have paracrine and autocrine roles.<sup>3</sup> Each member of the family of six high-affinity IGFBPs (IGFBP-1 to IGFBP-6) has a distinctive pattern of tissue expression.<sup>4</sup> The effect of IGFBPs on IGF availability to receptors depends on IGF-binding affinity,<sup>7</sup> interaction with other proteins, and a variety of post-translational modifications of the IGFBPs. Limited proteolysis of IGFBPs by tissue proteases reduces affinity and therefore increases IGF activity, while association with matrix proteins can stabilise IGF near cell surface receptors, which also enhances activity.<sup>4</sup> Human neuroblastoma cells, for example, secrete IGFBP-2 that is able to associate with cell membranes.<sup>17</sup> These cells rely on autocrine stimulation by IGFs and, when exposed to fibroblast growth factor (FGF) a protease is induced that cleaves IGFBP-2 and results in increased IGF activity. In addition, the IGFBPs have IGF-independent actions, for example the interaction of IGFBP-2 with the  $\alpha 5 \beta 1$  integrin via an arginyl-glycyl-aspartyl (RGD) domain promotes glioma cell migration.<sup>18</sup> The IGFBPs are structurally related to a superfamily of proteins<sup>19</sup> which do not bind IGFs and are beyond the scope of this review.

#### *GH/IGF expression and regulation in the nervous system*

Insulin-like growth factor I and IGF-II are widely expressed in nervous tissue from early embryonic life.<sup>20</sup> Understanding of the tempo-spatial expression of IGFs in brain is primarily derived from studies in rodents. Insulin-like growth factor I is widely expressed in brain, in neurons and glial cells.<sup>21</sup> At all stages of development, higher levels of IGF-I expression are associated with proliferating neural precursors.<sup>20</sup> Insulin-like growth factor II is predominantly expressed in mesenchymal tissues. In rodents, IGF-II expression is highest during

embryonic development, declines with age and is restricted to the meninges and choroid plexus in the adult.<sup>22</sup> Circulating GH is produced by the anterior part of the pituitary that derives embryonically from the ectoderm and is linked functionally to the nervous system by a system of capillary loops and sinusoids, known as the hypophyseal-portal circulation. GH-releasing hormone (GHRH) and somatostatin, which are secreted by hypothalamic neurons into the hypophyseal-portal circulation, are important peptides regulating the synthesis and pulsatile release of pituitary GH.<sup>16</sup> GH crosses the blood-brain barrier and IGF-I expressed in brain may be regulated by GH in a region-specific manner. In adult male rats, GH administration increases IGF-I expression in hypothalamus, cerebellum and hippocampus.<sup>23</sup> Cell- and tissue-specific effects are observed, with no change in IGF-I expression in cerebral cortex in response to GH in that study. In addition to pituitary, GH is expressed in nervous tissues. GH immunoreactivity has been detected in the rat amygdaloid nucleus and hypothalamus and increases after hypophysectomy.<sup>24</sup> Growth hormone and IGF-I are both expressed in the hippocampus of GH-deficient mice.<sup>25</sup> However overexpression of GH in mouse hippocampus is associated with only a modest change in local IGF-I expression.<sup>26</sup>

Insulin-like growth factor inhibits GH secretion through endocrine negative feedback, crossing the fenestrated sinusoid capillaries of the anterior pituitary, and inhibiting spontaneous and GHRH-stimulated GH release by somatotrophs.<sup>16</sup> It is also possible that there is negative feedback by IGF-I on GHRH in the hypothalamus. The blood-brain barriers regulate passage of substances, including IGFs,<sup>2</sup> through specific transport mechanisms, from the systemic circulation into brain parenchyma (Figure 1B) and from the choroid plexuses into cerebrospinal fluid (CSF). IGF uptake into CSF appears to be independent of IGF1R and IGFFBPs<sup>27</sup> and, although also produced locally, brain IGF-I levels are determined to some extent by circulating concentrations.<sup>28</sup> Insulin-like growth factor passage into brain is triggered by local neuronal activity through a mechanism that includes vasodilatation and increased IGFBP-3 protease activity generating fragments with lower affinity for IGFs.<sup>29</sup> Insulin-like growth factor is then more available to interact with the endothelial transporter low-density lipoprotein-related receptor (LRP)1. It has been shown that LRP2 (megalin), which participates in brain uptake of  $\beta$ -amyloid carrier proteins, also has a role in IGF-I transport across the choroid plexus and mediates IGF-I-induced clearance of  $\beta$ -amyloid.<sup>30,31</sup> Insulin-like growth factor II is also expressed in adult human brain.<sup>32</sup> Cerebrospinal fluid provides a proliferative niche for supraventricular neural progenitors,<sup>33</sup> and there is evidence that IGF-II acting via IGF1R is an important determinant of CSF activity on these stem cells.<sup>34</sup> In songbirds (canaries and zebrafinches), IGF-II is expressed in neurons in areas of brain responsible for song, and correlates with neuronal plasticity.<sup>35</sup>

Studies of transgenic and knockout mice have indicated that IGF-I and IGF-II have distinct nervous system functions.<sup>36</sup> *Igf1* overexpressing mice have increased postnatal brain growth,<sup>37</sup> while *Igf2* overexpression appears to have no effect on brain growth.<sup>38</sup> Mice with *igf1* deficiency have impaired neuronal somatic and dendritic growth<sup>39</sup> but no evidence of neurological dysfunction and a degree of myelination that is proportionate to brain mass,<sup>40</sup> while *igf2*<sup>-/-</sup> mice have no apparent changes in brain morphology<sup>41</sup> and are less susceptible to hippocampal neurodegeneration<sup>42</sup> compared to controls. Insulin-like growth factor I is naturally cleaved in brain<sup>32</sup> and in the circulation<sup>43</sup> to a variant that lacks the N-terminal tripeptide glycine-proline-glutamate (GPE) and has reduced affinity for IGFFBPs.<sup>44</sup> IGFBP inhibits this cleavage of IGF-I.<sup>45</sup> Centrally, the GPE tripeptide can also cross the blood-brain barrier to reach the CSF, where it has a longer half-life than in plasma associated with reduced susceptibility to proteolytic degradation.<sup>43</sup> In retinal glial cells, both the truncated IGF-I variant and the cleaved tripeptide have mitogenic activity.<sup>46</sup> GPE stimulates potassium-induced acetylcholine release in rat cortical slices<sup>47</sup> and has neuroprotective effects in hippocampus and striatum.<sup>43,48,49</sup> GPE inhibits gonadotrophin-releasing hormone secretion through antagonism at N-methyl-D-aspartate (NMDA) receptors.<sup>45</sup>

### *IGF receptors and signalling in the nervous system*

The effects of IGFs on cell growth/apoptosis and metabolism are through IGF1R and IR which are ubiquitously expressed in the nervous system.<sup>50,51</sup> IGF1R null mice have generalised growth retardation including brain, characterised by reduced neuronal fibres and neuroglial cell cytoplasm but increased nerve cell number.<sup>52</sup> Mice with neuron-specific deletion of IR have normal brain size and development, but develop obesity and mild insulin resistance.<sup>53</sup> This central metabolic effect may be due to the action of local insulin which is also expressed in brain.<sup>50,54</sup> IGF2R is widely distributed in brain<sup>55</sup>; however, role in regulating IGF-II availability in human brain has not been elucidated.

In addition to feedback inhibition of GH, IGF-I acts directly to increase insulin sensitivity at the post-receptor level.<sup>15</sup> IGFs also act in concert with other growth factors to influence nervous system function. The effect of FGF-2 withdrawal in promoting neuronal differentiation from stem cells is mediated by IGF-I,<sup>56</sup> and pre-treatment with FGF-2 increases IGF1R expression.<sup>57</sup> In rodent astrocytes, IGF-I secretion is stimulated by epidermal growth factor (EGF) and IGF1R blockade reduces the action of EGF on cell replication.<sup>58,59</sup> In a human neuroblastoma cell line, IGF-II stimulates cell growth in the presence of EGF.<sup>60</sup> Insulin-like growth factor I signalling pathways interact with those of sex steroids in the neuroendocrine hypothalamus and also in the hippocampus in the control of neurogenesis and synaptic plasticity.<sup>61</sup> The effect of

IGF-I on oestrogen signalling in brain is cell type-specific and oestrogen receptor isoform-specific.<sup>62</sup> When the IGF-I gene is delivered to the medial basal hypothalamus in female rats, serum luteinising hormone levels are higher, probably due to enhanced oestrogen positive feedback on GnRH production, and ovarian function is prolonged.<sup>63</sup> The IGF system interfaces with the brain-derived neurotrophic factor (BDNF) system. In rats, the exercise-induced increase in learning recall, and hippocampal BDNF expression and signalling is prevented when IGF1R-blocking antibody is delivered to the hippocampus.<sup>64</sup>

### *IGFBPs in the nervous system*

In studies with transgenic mice, early null mutations of IGFBPs appeared to have no brain phenotype, and it was suggested that this indicated 'redundancy' in the system.<sup>36</sup> Earlier studies of the overexpression of IGFBPs have shown little or inconsistent effects on the nervous system.<sup>36</sup> However, there are exceptions. Transgenic mice overexpressing IGFBP-1 in brain have impaired brain growth and reduced glial cell proliferation in response to injury.<sup>65,66</sup> While IGFBP-1 is not normally expressed in brain, endocrine IGFBP-1 can have an effect on brain development, with reduced cortex and hippocampus development in mice with liver-specific overexpression of IGFBP-1 during foetal life.<sup>67</sup> When IGFBP-6 is overexpressed in brain, mice have reduced cerebellum size and weight,<sup>68</sup> dysregulation of energy homeostasis and obesity.<sup>69</sup>

Despite their importance in regulating IGF action, the roles of IGFBPs in brain are less well studied than IGF-I. Insulin-like growth factor binding protein 5 is one of the major IGFBPs expressed in brain. It is found in neurons throughout the cerebral cortex, colocalised with cells that secrete kallikreins that proteolyse IGFBP-5.<sup>70</sup> There is also evidence that IGFBP-2 has an important role in the nervous system. Insulin-like growth factor binding protein 2 is abundant in brain and is highly expressed by astrocytes in the cortex.<sup>71</sup> During depolarisation, IGFBP-2 expression is upregulated in astrocytes.<sup>72</sup> NMDA receptors may be responsible for this upregulation. Along with IGF-II, IGFBP-2 is synthesised and secreted by meningeal cells.<sup>73</sup> While IGFBP-2 has been shown to inhibit oligodendrocyte precursor cell survival and differentiation *in vitro*,<sup>74</sup> there is evidence that cell membrane-associated IGFBP-2 can increase IGF activity.<sup>17</sup> It has been suggested that IGFBP-4 is involved in the maintenance of cerebellar plasticity<sup>75</sup> and in microtubule functions in astrocytes.<sup>76</sup> In transgenic mice overexpressing tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), changes in the IGF system are seen consistent with reduced IGF availability with increases in IGFBP-3 and IGFBP-4 protein expression, along with reduced IGFBP-5 and IGF-I in radial glial and Purkinje cells.<sup>77</sup>

Cell lines from neuroblastomas, which are malignant childhood tumours derived from neural crest stem cells, are often used as models for exploring the role of IGFs and IGFBPs.

Insulin like growth factor I and IGF-II act as paracrine/autocrine signals via IGF1R in human neuroblastoma cell lines,<sup>78</sup> including those comprised of epithelial Schwann cells,<sup>60</sup> and may stimulate growth of primary tumours in concert with other growth factors. IGFBP-2<sup>78</sup> and IGFBP-5<sup>79</sup> are also expressed in neuroblastoma cells and can stimulate or inhibit cell growth depending on their concentration or the presence of IGFs<sup>79</sup> or proteases that alter IGF binding affinity.<sup>17</sup> IGFBP-2 is recognised as an oncogene in a variety of human cancers<sup>80</sup> including those of the nervous system: gliomas<sup>81–86</sup> and meningiomas<sup>87,88</sup>. Interaction of IGFBP-2 with the  $\alpha 5\beta 1$  integrin via its RGD domain has been implicated in glioma progression<sup>81</sup> and migration.<sup>18</sup> Higher serum IGFBP-5 levels are associated with glioblastoma recurrence.<sup>89</sup>

### **Normal Development and Ageing**

The IGF system has an essential role in normal growth, development and maintenance of the nervous system.<sup>20,33,90,91</sup> From week 3 of embryonic life, neural stem cells proliferate, migrate from the subventricular zone, and differentiate in a highly complex manner, producing neurotransmitter and neurotrophic factors and processes (axons and dendrites) that allow synaptic interconnections. Apoptotic cell death is an important mechanism for eliminating neural progenitor cells with a transient role in nervous system development. In the postnatal period, neuronal production and migration is largely complete; however, neurogenesis continues throughout adulthood in specific regions of the brain: the dentate gyrus of the hippocampus (important for learning and memory), the supraventricular zone (cells migrate to the olfactory bulb), and the striatum (voluntary motor control).<sup>92,93</sup> Glial cell (oligodendrocytes, astrocytes and microglia) proliferation, migration and maturation continues throughout childhood and glial progenitors persist in adult brain and can differentiate in response to injury, and glial cell apoptosis continues into postnatal life.<sup>94</sup>

### *IGFs in development and maintenance of the nervous system*

Local paracrine/autocrine sources of IGFs are essential for normal nervous system development. Children with reduced endocrine IGF-I due to GH insensitivity generally have normal cognitive function,<sup>95</sup> despite craniofacial abnormalities,<sup>96,97</sup> while those with IGF-I deletion<sup>98</sup> or IGF-I receptor mutations<sup>99</sup> and therefore reduced paracrine/autocrine IGF-I activity, have microencephaly and cognitive impairment. Nevertheless endocrine sources of IGFs also have important roles. In pre-term infants, circulating levels of IGF-I and IGFBP-3 postnatally are positively associated with brain volumes.<sup>100</sup> Early treatment of children with GH insensitivity with IGF-I is reported to prevent cochlear hearing loss.<sup>101</sup> Less is known about the role of IGF-II in nervous system development. Maternally imprinted, IGF-II gene hypermethylation has been identified as a potential risk factor for neural tube

defects.<sup>102</sup> Paternal folate deficiency in rats has also been shown to influence brain IGF-II methylation despite adequate maternal folate during gestation.<sup>103</sup>

Insulin like growth factor I and IGF1R are expressed early in development throughout the brain.<sup>20</sup> In rats, neonatal undernutrition increases expression of IGF-I and IGF1R in cerebellum and hypothalamus, and decreases IGFBP-2 in hypothalamus in the perinatal period.<sup>104</sup> In this way, in the face of reduced endocrine IGF-I production, the paracrine/autocrine availability of IGF-I at a time of rapid brain growth and development is likely to be optimised. There is substantial evidence from mutant mouse models<sup>36</sup> that IGF-I promotes neuron numbers, through increased proliferation and reduced apoptosis, as well as process outgrowth and synaptogenesis, throughout nervous system development. Overexpression of IGF-I in the striatum of adult rat brain, for example, induces migration of adult neuronal precursor cells.<sup>105</sup> There is evidence that the proliferating effect of IGF-1 is via RAF/MEK/ERK signalling, while the differentiating effects involve PI3K/Akt pathways.<sup>106</sup> Insulin like growth factor I signalling interacts with other growth factor pathways that are important in the nervous system. These include growth factors (eg, FGFs, EGF and vascular endothelial growth factor [VEGF]) and neurotrophic factors (eg, BDNF), which together maintain proliferation of neural stem cells, and neurotransmitters and transcriptional factors, which regulate the neurogenic process.<sup>56,107,108</sup> Studies in rodents suggest that prenatal exposure to steroids<sup>109,110</sup> and neonatal repetitive maternal separation<sup>111</sup> alters IGF system expression in developing brain in ways that may increase susceptibility to cell damage. These studies have potential implication for management of pre-term infants.

Oligodendrocyte differentiation is associated with increased myelin expression and the production of trophic factors that are important for neuronal survival and axonal integrity. Insulin like growth factor I enhances oligodendrocyte progenitor cell differentiation and therefore myelination.<sup>112,113</sup> There is substantial evidence that IGFs play a role in oligodendrocyte differentiation and survival, and myelin synthesis<sup>36</sup> as well as Schwann cell survival and motility.<sup>114,115</sup> Microglia are the innate immune cells of the brain.<sup>116</sup> Following an epileptic seizure, IGF-I expression in microglia is upregulated<sup>117</sup> and may play a role in minimising cell damage. Astrocytes provide physical and nutrient support, and participate in maintaining blood-brain barriers and modulating synaptic transmission.<sup>94</sup> Insulin like growth factor I is increased in activated astrocytes<sup>118</sup> and regulation of mitochondrial function and redox status by IGF-I is essential in the maintenance of astrocyte function.<sup>119</sup>

### *Ageing and cognitive function*

Insulin/IGF signalling pathways are phylogenetically conserved<sup>120</sup> and are central to the ageing process.<sup>121</sup> Reduced function of these pathways has been shown to extend survival

in rodents.<sup>122,123</sup> There is increasing evidence that changes in activity of splicing factors are involved in the ageing phenotype. Exercise-induced changes in the IGF-I splice variant mechano growth factor (MGF) have been shown to decrease with age.<sup>124</sup> IGF1R variants have been described that are more prevalent in Ashkenazi Jewish centenarians<sup>125</sup> and which are reduced-function mutations.<sup>126</sup>

IGF signalling is involved in adult hippocampal neurogenesis.<sup>127,128</sup> Hippocampal neuroblasts decline with age, however this decrease is less pronounced in humans, compared to mice<sup>93</sup> and the cognitive decline may be largely due to changes in neural stem cell activity rather than number.<sup>129</sup> Glial cell numbers do not appear to decline with age.<sup>130</sup> With ageing there is a decline in endocrine IGF-I,<sup>131</sup> which is a candidate frailty biomarker.<sup>131,132</sup> Brain IGF-I and IGF signalling is also reduced during ageing.<sup>131,133</sup> In addition to the GH/IGF system, other age-related changes in growth factors have been linked to changes in neurogenesis, including loss of FGF-2 and VEGF.<sup>134,135</sup> Studies in rodents have demonstrated close links between IGF-I, hippocampal neurogenesis and cognitive function. Intracerebroventricular infusion of IGF-I ameliorates age-related decline of hippocampal neurogenesis in rats.<sup>136</sup> It has been suggested that reduced hippocampal neurogenesis contributes to the pathophysiology of depression.<sup>90</sup> Mice with specific knockout of hippocampal IGF-I have been shown to have a depressive phenotype that is not rescued by endocrine IGF-I.<sup>137</sup>

In mice, the effects of physical activity on hippocampal neurogenesis and cognition are associated with circulating IGF-I levels.<sup>138</sup> In rats, there is evidence that aerobic and resistance training increase learning and spatial memory through divergent molecular pathways: resistance training acts via the IGF-I/IGF1R/Akt pathway in hippocampus.<sup>139</sup> Physical activity also increases brain uptake of endocrine IGF-I.<sup>140</sup> In adolescent humans exercise increases both IGF-I and BDNF.<sup>141</sup> In adults increased temporal lobe functional connectivity in response to exercise is associated with increases in circulating IGF-I, BDNF and VEGF.<sup>142</sup> There is experimental evidence that hippocampal increases in BDNF are more important than changes in peripheral levels of IGF-I and BDNF,<sup>143</sup> and that IGF-I interacts with BDNF and VEGF signalling pathways in exercise-related changes to hippocampal function.<sup>64,144,145</sup>

In humans, studies of the relationship between serum IGF-I and cognitive function or decline in cognitive function are conflicting. In a large prospective study, higher levels of serum IGF-I were associated with better cognitive performance in women but not men.<sup>146</sup> Insulin like growth factor I treatment in postmenopausal women has no effect on memory.<sup>147</sup> Overall, serum IGF-I is not considered a useful biomarker of cognitive decline in the ageing brain,<sup>148</sup> and there may be a U-shaped relationship between IGF-I and cognitive function. In females with exceptional longevity, lower serum IGF-I is associated with better cognition.<sup>149</sup> In adult patients with GH deficiency, however, cognitive impairment which contributes to reduced

quality of life is ameliorated by GH replacement.<sup>150</sup> Rodent models with GH deficiency or resistance have a delayed age-induced decline in memory retention.<sup>151,152</sup> In adult rats, peripheral administration of GH stimulates hippocampal neurogenesis both in the presence<sup>153</sup> and absence<sup>154</sup> of GH deficiency. It seems likely that this effect of GH is mediated by endocrine IGF-I; peripheral administration of IGF-I also stimulates hippocampal neurogenesis.<sup>155</sup>

Insulin and IGF-I are nutrient-sensitive signalling pathways and have key roles in energy metabolism, including that of neural stem cells.<sup>156,157</sup> In rodents, IGF-I regulates glucose metabolism in developing<sup>158</sup> and aged<sup>159</sup> brain. Brain is also an important target for insulin actions with effects on neuronal survival and synaptic plasticity, particularly in the hippocampus where IR are abundant.<sup>160</sup> There is also evidence that IGF-II, given subcutaneously, is neuroprotective in ageing rats.<sup>161</sup> Compared to IGF-I, differences in affinity for IGF1R/IR of IGF-II and its production by the choroid plexus indicate that it might have a distinct role in the nervous system.<sup>162</sup> The role this plays in the choroid plexus alongside IGF-I, expression of which declines with ageing<sup>163</sup> should be further explored. Insulin like growth factor II is also expressed in the leptomeninges and parenchymal vasculature.<sup>164</sup> Expressed by neural stem cells, it has been suggested that IGF-II from these cells and from the choroid plexus has an important role in maintaining neurogenesis in the supraventricular zone.<sup>162</sup> Insulin like growth factor II may also play a key role in maintenance of neurogenesis in the hippocampus. An effect of IGF-II on memory enhancement is supported by experimental evidence.<sup>165</sup> Interestingly, IGF2R overexpression is associated with increased  $\beta$ -amyloid generation.<sup>166</sup> While this is likely due to an effect on endocytic pathways, the role of increased IGF-II disposal has not been explored.<sup>167</sup>

### Neurodegenerative Disorders

Brain regions with the capacity for neurogenesis are prone to neurodegenerative disease. Loss of neurons and their functions, particularly cholinergic and dopaminergic neurons, results in impairments ranging from cognitive abilities to coordination and mobility.<sup>168–170</sup> Alzheimer disease (AD), Parkinson disease (PD), and Huntington disease (HD) all cause a dementia that is distinct from the physiological decline that occurs with ageing. Despite different distinct pathological processes, many of the hallmark features are identical, eg, depression and anxiety, loss of cognitive function and olfactory dysfunction. There is compelling evidence that inflammation is key to the aetiology or pathogenesis of these neurodegenerative disorders.<sup>169</sup> In each, protein misfolding and aggregation lead to activation of neuroinflammatory processes.<sup>121</sup> Activated glial cells produce a microenvironment of reactive oxygen species (ROS) and pro-inflammatory mediators contribute to neuronal damage and death in a vicious cycle.<sup>169</sup> Reduced IGFBP expression in lipopolysaccharide-activated microglia<sup>171</sup> might play an important role in increasing paracrine/autocrine IGF availability.

While neurotrophic factors, including IGF-I, are increased in activated astrocytes, this may be insufficient to exert the required neuroprotective effect.<sup>118</sup>

Obesity is associated with a chronic inflammatory state that is considered a contributor to the prevalence of neurodegenerative disorders, with IGF/insulin resistance being the possible link.<sup>169</sup> There is substantial evidence that IGF/insulin signalling and cross-talk with other signalling pathways are involved in the processes of neurodegeneration.<sup>121,127,172,173</sup> The regions of brain with neurogenic capacity are highly vascular. In rodents there is evidence that IGF-I is required for vascular remodelling in adult brain.<sup>174</sup> Age-related cerebrovascular changes that also contribute to the neurodegenerative pathology.<sup>175</sup> These regions are highly vascular and multiple systemic factors including IGF-I and IGF-II may play a role.<sup>176</sup>

### Alzheimer disease

Alzheimer disease is the most common of the neurodegenerative dementias. The two hallmarks of the disease are neuritic plaques, formed by the extracellular accumulation of abnormal  $\beta$ -amyloid protein,<sup>177</sup> and intracellular neurofibrillary tangles, composed of hyperphosphorylated tau protein.<sup>178</sup> Plaques and neurofibrillary tangles both contribute to glial cell activation and neuroinflammation that influence AD pathogenesis and neuronal loss.<sup>170,179</sup> Glutamate is the most important excitatory neurotransmitter and is involved in neuronal growth and synaptic plasticity.<sup>180</sup> Glutamate influences  $\beta$ -amyloid production, and  $\beta$ -amyloid is itself an activator of glutamatergic receptors of the NMDA type that are essential for both long-term potentiation (LTP) and long-term depression (LTD) and are therefore crucial in learning and memory. It is argued that interference with NMDA receptors by abnormal accumulation of  $\beta$ -amyloid and the ability of  $\beta$ -amyloid to increase tau phosphorylation underpin synaptic loss and cognitive decline in AD patients.<sup>181</sup>

The  $\beta$ -amyloid precursor protein (APP) is cleaved by membrane-bound  $\beta$ - and  $\gamma$ -secretases into  $\beta$ -amyloid, the longer forms of which are more likely to be deposited. Monomeric forms of  $\beta$ -amyloid are less toxic and are able to activate insulin/IGF pathways.<sup>182</sup> While IGF-I has been shown to rescue rat hippocampal neurons from the toxicity induced oligomeric forms of  $\beta$ -amyloid *in vitro*,<sup>183,184</sup> it also increases the extracellular concentration of  $\beta$ -amyloid by promoting its secretion and inhibiting its degradation.<sup>185</sup> Neuronal death in AD is strongly associated with mitochondrial dysfunction<sup>186</sup> including increased ROS production, decreased mitochondrial enzymes and increased oxidative damage. It has been argued that ageing, the most important non-genetic risk factor for AD development, does so largely via mitochondrial dysfunction, though levels of  $\beta$ -amyloid degrading enzymes also decline with age.<sup>187</sup>

There is an increased prevalence of AD in type 2 diabetes mellitus in humans<sup>188</sup>; however, this association is likely to be confounded by the presence of cerebrovascular pathology which reduces the number of AD lesions required for the

manifestation of clinical dementia.<sup>189</sup> Insulin signalling appears to be involved in both  $\beta$ -amyloid peptide deposition and tau phosphorylation,<sup>190,191</sup> and defective insulin signalling is thought to play a key role in disease pathogenesis.<sup>192,193</sup> The finding of altered brain expression of insulin and IGFs, and their receptors has led to the suggestion that AD be labelled 'type 3 diabetes'.<sup>194</sup> Indeed functional proteomics suggests that the link between AD and diabetes relates to insulin/IGF signalling. Using tissue samples from brains of patients with AD, compared to tissue from normal individuals, insulin resistance in hippocampus and cerebral cortex was found to be associated with IGF-I resistance and cognitive decline.<sup>195</sup> Expressions of IGF1R and IR are increased in AD neurons in the temporal cortex while that of IR substrate (IRS)-1 and IRS-2 are decreased.<sup>196</sup> Some studies have proposed a relationship between endocrine IGF-I and the risk of AD; however, in a meta-analysis of nine studies comprising 1639 individuals, no link between serum IGF-I and AD was demonstrated.<sup>197</sup> There is one report of an association between an IGF-I polymorphism and late-onset AD in a Chinese population.<sup>198</sup>

Most of our understanding of the role of insulin and IGFs in AD has come from studies in rodents. Intracerebrospinal streptozotocin in mice induces AD-like changes in pathology and behaviour and is associated with reduced brain expression of insulin, IGFs and reduced IGF1R binding and signalling.<sup>199,200</sup> In mice, brain-specific IGF-I knockout is associated with hyperphosphorylation of tau protein,<sup>201</sup> while blockade of IGF1R function in the choroid plexus of rats is associated with AD-like neuropathology.<sup>202</sup> Transgenic models of AD have been developed including mutations that target APP or the tau protein.<sup>203,204</sup> When mice expressing mutant APP are crossed with those genetically predisposed to diabetes, development of cognitive dysfunction is accelerated.<sup>205</sup> In these animals, in addition to reduced brain insulin signalling, marked vascular inflammation was observed despite no change in  $\beta$ -amyloid deposition. Presenilin, a crucial component of the  $\gamma$ -secretase complex, also controls IR expression.<sup>206</sup> Mice overexpressing pancreatic  $\beta$ -cell IGF-II develop hyperinsulinaemia, and co-expression of mutations of both APP and presenilin-1 genes exacerbates the development of peripheral insulin resistance, with no increase in brain insulin or  $\beta$ -amyloid deposition.<sup>207</sup> Mice expressing mutant APP have reduced CSF/serum IGF-I ratio and low serum IGF-I is an early biomarker of AD onset.<sup>208</sup> When mutations of both APP and presenilin-1 genes are combined with endocrine IGF-I deficiency due to targeted deletion of hepatic IGF-I, amyloid plaque formation occurs earlier.<sup>209</sup> On the other hand, reduction in serum IGF-I through protein restriction, is associated with reduced AD neuropathology in mice expressing mutant APP, presenilin-1 and tau proteins.<sup>210</sup>

As has been observed in human brain tissue, brain slices from mice expressing mutant APP have increased IGF1R expression and reduced Akt response to IGF-I<sup>211</sup> and, when

crossed with *igf1r* +/-, a reduction in  $\beta$ -amyloid-associated behavioural impairment associated with the sequestration of  $\beta$ -amyloid aggregates of lower toxicity has been observed.<sup>212</sup> The protective effect of neuronal IGF-I resistance is supported by the observation that, in a neuron-targeted IGF1R knockout combined with the APP mutation, APP processing is decreased and  $\beta$ -amyloid accumulation is reduced<sup>213</sup> and, when combined with mutant APP and presenilin-1, there is improved spatial memory, fewer amyloid plaques and less neuroinflammation.<sup>214</sup> Paradoxically, in the same model, systemic delivery of IGF-I ameliorates the AD-like changes and increases transport of  $\beta$ -amyloid/carrier protein complexes through the choroid plexus barrier.<sup>215</sup> Taken together, these studies suggest that, while reduced IGF action centrally is associated with improved AD pathology, increased peripheral IGF availability is neuroprotective through increased  $\beta$ -amyloid clearance. In ageing mice with a targeted deletion of hepatic IGF-I, and therefore reduced endocrine IGF-I, there is a premature increase in brain  $\beta$ -amyloid, and administration of IGF-I increases clearance and reduces  $\beta$ -amyloid levels.<sup>216</sup> In this research, IGF-I was found to affect the permeability of the blood-brain barrier to carrier proteins such as albumin and transthyretin. However other studies, using multiple *in vivo* models including APP-overexpressing mice, have shown no impact of peripheral IGF-I on brain  $\beta$ -amyloid levels or the phosphorylation state of tau.<sup>217</sup> Furthermore in rats intracerebroventricular IGF-I prevents the deleterious effect of coadministered  $\beta$ -amyloid on the somatostatinergic system in the temporal cortex.<sup>218</sup> The N-terminal tripeptide also has protective effects on the somatostatin system in temporal cortex of  $\beta$ -amyloid treated rats, through modulation of calcium and glycogen synthase kinase 3 $\beta$  (GSK3 $\beta$ ) signalling.<sup>219</sup>

In addition to considerations of endocrine versus tissue IGFs, an understanding of the factors regulating expression and action in different cell types is required in order to unravel the role of the system in AD. IGF-I and insulin stimulate neuronal secretion of  $\beta$ -amyloid and reduce its degradation,<sup>185</sup> while also having a neuroprotective role,<sup>183</sup> however expression and action of IGF-I and insulin are reduced in AD. As the AD pathology progresses, astrocytes also have reduced expression of insulin and IGF signalling pathways particularly in individuals expressing the *APOE $\epsilon$ 4* allele.<sup>220</sup> Insulin reduces APP levels in individuals without the *APOE $\epsilon$ 4* allele.<sup>221</sup> In a co-culture system, impaired IGF-I signalling in human astrocytes is associated with reduced ability to protect neurons from oxidative stress.<sup>222</sup> Oxidative stress has been identified as an important link between AD and insulin resistance,<sup>223</sup> with Forkhead box class O (FoxO) transcription factors as candidates for the molecular integrative link.<sup>224</sup> Insulin like growth factor I inactivates and displaces FoxO3 from calcineurin in activated astrocytes, with reduced inflammatory signalling associated with reduced AD phenotype in mice with mutations of both APP and presenilin-1 genes.<sup>225</sup>

### Parkinson disease

Parkinson disease is a neurodegenerative disorder characterised by significant motor impairments, including bradykinesia, muscular rigidity, tremor and postural instability. However non-motor signs and symptoms, such as impaired olfaction, cognitive impairment and depression, may precede the classical motor signs by many years<sup>226</sup> and indicate early involvement of the olfactory bulb and hippocampus in the disease. The hallmark of PD is the gradual, selective loss of dopaminergic neurons of the substantia nigra pars compacta region and the aggregation of misfolded  $\alpha$ -synuclein protein forming insoluble cytoplasmic inclusions (Lewy Bodies).<sup>227</sup> Individuals with the rare familial forms have mutations of  $\alpha$ -synuclein.<sup>228</sup> Misfolded  $\alpha$ -synuclein specifically induces free radical production in dopaminergic neurons, triggering apoptosis,<sup>229</sup> and there is also a strong association between PD and mitochondrial dysfunction.<sup>230</sup> Other genes associated with PD encode proteins involved in cellular trafficking and protein turnover.<sup>231</sup> Chronic exposure of human neuroblastoma cells to rotenone, an inhibitor of complex I of the mitochondrial electron transport chain, induces many of the biochemical features of PD.<sup>232</sup> Interestingly, in peripheral lymphocytes, IGF-I has a protective effect on rotenone-induced apoptosis.<sup>233</sup>

A meta-analysis of five studies with 166 patients showed that IGF-I levels were higher in drug naive patients with PD compared to 323 healthy controls.<sup>234</sup> However, in patients with PD, lower circulating IGF-I concentrations are associated with poor cognitive performance<sup>235,236</sup> and have been shown to predict decline in cognitive function after a 2 year follow-up.<sup>237</sup> Nevertheless it is clear that confounding factors, such as age and obesity limit the use of IGF-I as a predictive marker.<sup>238</sup> Association of an IGF-I gene polymorphism with PD has been demonstrated in a Chinese population<sup>239</sup> and is the same polymorphism as that associated with AD in the same population.<sup>198</sup> In postmortem brain tissue, IGF-I expression is increased in frontal cortex in PD compared to controls, while insulin, IGF-II, IR, IGF1R and IGF2R are reduced in white matter and amygdala.<sup>240</sup>

Dopamine-denervated striatum, using 6-hydroxydopamine delivered unilaterally, induces a Parkinson's-like disease in rats. Using this model, IGF-I, combined with FGF, improves dopamine neuron survival and behavioural outcome in response to transplants of human foetal tissue strands.<sup>241</sup> Insulin like growth factor I expression using a lentiviral vector had neuroprotective effects *in vitro*; however, after intra-striatal delivery to 6-hydroxydopamine treated rats, no effect on survival of dopaminergic cells or behaviour was observed.<sup>242</sup> This may have been due to insufficient concentrations of delivered IGF-I. Using high concentrations of dopamine to induce neurotoxicity *in vitro*, apoptosis is significantly reduced by IGF-I in primary rat cerebellar cells and a human neuroblastoma cell line.<sup>243</sup>

Later studies have demonstrated that the PI3K/Akt pathway is critical for the *in vivo* action of IGF-I and also mediates the protective effect of oestrogen on dopaminergic neurons in PD rat models.<sup>244</sup> Peripheral administration of the N-terminal tripeptide, that has been shown to modulate GSK3 $\beta$ <sup>219</sup> in a model of AD, also improves functional deficits in PD rats.<sup>245</sup> The involvement of PI3K/Akt/GSK3 $\beta$  signalling pathways in PD has recently been reviewed.<sup>246</sup>

### Huntington disease

Huntington disease is an autosomal progressive neurodegenerative disease characterised by chorea, abnormal voluntary movements, and cognitive and psychological dysfunction.<sup>247,248</sup> A key characteristic of the disorder is the aggregation of mutant huntingtin protein in intranuclear inclusions in the GABAergic medium spiny neurons of the striatum.<sup>249</sup> This is due to an expanding CAG triplet repeat in the gene, the length of which contributes approximately 70% of the variance in age of onset of symptoms.<sup>250</sup>

In a longitudinal study of patients with HD, higher levels of total circulating IGF-I at baseline were associated with a higher degree of cognitive impairment and predicted decreases in cognitive scores over a 3.5-year follow-up.<sup>251</sup> While higher insulin levels were also associated with lower cognitive scores, they were not predictive of change in cognitive function. On the other hand, in humans, concentrations of the acid labile subunit of the ternary complex are reduced.<sup>252</sup>

Rodent models of HD, including striatal lesioning using mitochondrial toxins or quinolinic acid and mice expressing a mutant huntingtin transgene (eg, R6/1, R6/2, N171-82Q and YAC128), have been used to further explore the role of the IGF system. In R6/1 HD mice, histone deacetylase has been identified as a switch between neuroprotection and neuronal death with IGF-I inhibiting the neurotoxic effect.<sup>253</sup> When combined with heterozygous *Igf-1* knockout, there are some beneficial effects on the HD phenotype in female N171-82Q HD mice, but some detrimental effects in males, and no effect on survival.<sup>254</sup> In R6/1 HD mice running-induced hippocampal neurogenesis is associated with reduced Akt signalling despite increased serum IGF-I.<sup>255</sup> On the other hand, intranasal IGF-I rescues the YAC128 phenotype.<sup>256</sup> The neuroprotective effect of cannabigerol in R6/2 and in mice given the mitochondrial toxin 3-nitropropionate is associated with modest improvements in striatal expression of BDNF and IGF-I.<sup>257</sup> Ablation of caspase-6 in YAC128 HD mice reverses the HD phenotype and is associated with weight loss and reduced serum IGF-I.<sup>258</sup> Administration of the N-terminal IGF-I tripeptide also prevents HD neuropathology in rats with lesions of the striatum induced by quinolinic acid.<sup>48</sup> Atypical diabetes develops in 70% of R6/2 HD mice<sup>259</sup> and is associated with dysregulated gene expression and intranuclear inclusions in pancreas.<sup>260,261</sup> Blood glucose levels are restored by IGF-I infusion in these mice.<sup>262</sup>



Patients with HD are more likely to develop diabetes, and have impaired insulin secretion and peripheral insulin resistance.<sup>261</sup>

In studies using transfected striatal neurons *in vitro*, it was found that IGF-I blocks mutant huntingtin-induced cell death and decreased formation of intranuclear inclusions.<sup>263</sup> BDNF, which also reduced apoptosis, did not block the formation of intranuclear inclusions.<sup>264</sup> Striatal cell lines and primary cortical cultures derived from huntingtin knock-in mice have mitochondrial dysfunction that is ameliorated by insulin and IGF-I.<sup>265,266</sup> Impaired mitochondrial function appears also to have an important pathological role in HD in peripheral tissues. In lymphoblasts derived from HD patients, reduced energy metabolism and mitochondrial dysfunction are associated with reduced Akt and ERK activation and can be rescued with IGF-I or insulin.<sup>267</sup>

### Neuroprotective and Neurotrophic Roles

While there is convincing evidence that the IGF system has specific roles in the neurodegenerative dementias through effects on hippocampal neurogenesis, it has been suggested that more general neurotrophic and neuroprotective effects of IGF-I might be important in a range of other disorders.<sup>268</sup> HIV is associated with dementia that relates to TNF $\alpha$  released by activated macrophages: IGF-I has an antiapoptotic effect on neurons exposed to medium from infected macrophages.<sup>269</sup> It is likely that the increase in IGF-I and BDNF after retinal stem cell transplantation in a rat model of glaucoma had a neuroprotective role.<sup>270</sup> A potential role for IGF-I as a therapeutic approach has been considered for amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), cerebrovascular disease and following trauma, and these are therefore reviewed briefly here.

#### *Amyotrophic lateral sclerosis*

Amyotrophic lateral sclerosis is a degenerative disease of upper and lower motor neurons that leads to progressive weakness in limb and bulbar muscle with ultimately respiratory failure. The pathogenesis of ALS remains unclear, but a number of factors have been suggested including evidence of oxidative damage to proteins,<sup>271</sup> lipids<sup>272</sup> and DNA.<sup>273</sup> In common with other neurodegenerative disorders, mitochondrial dysfunction<sup>274</sup> and protein aggregation involving superoxide dismutase 1 (SOD1)<sup>275,276</sup> and TDP-43<sup>277,278</sup> have been associated with ALS. The first proven cause of ALS was identified in individuals with mutations in SOD1<sup>279</sup> which involve a toxic gain of dysfunction<sup>280</sup> but beyond involvement in protein aggregation, the mechanism remains unclear. In an animal model of ALS, the SOD1G93A mouse, IGF1R is increased in reactive astrocytes in the central nervous system.<sup>281</sup> Retrograde viral delivery of IGF-I from muscle to motor neurons prolongs life and delays disease progress.<sup>282</sup> Neuroinflammatory responses are also implicated in ALS.<sup>283</sup> In the SOD1G93A

mouse, intrathecal treatment with IGF-I decreases macrophage invasion and activation of TNF $\alpha$  production in sciatic nerves and delivery of a vector to knockdown IGF-I increases sciatic nerve inflammation.<sup>284</sup> In the same mouse model, intraparenchymal spinal cord delivery of adeno-associated IGF-I partially rescues lumbar spinal cord motor neurons.<sup>285</sup> VEGF and IGF-I gene transfer in to cellular components of the ventricular system have similar, non-additive effect to delay motor decline and prolong survival.<sup>286</sup> Administration of IGF-I in another animal model with ALS features, the wobbler mouse, results in significant improvements in muscle strength and histopathology, although no changes in motor neurone numbers were observed.<sup>287</sup>

Patients with ALS have reduced circulating IGFs and insulin, and increased IGFFBPs<sup>288</sup>; however, the potential for use of IGFs and IGFFBPs in therapy is still considered worthwhile.<sup>289,290</sup> While there have been randomised controlled trials involving the use of IGF-I in humans, these do not provide strong evidence supporting its effectiveness.<sup>6</sup> There is a possibility that upregulation of IGFBP-5 might play a role in the response to IGF-I in these disorders.<sup>291</sup>

#### *Multiple sclerosis*

Multiple sclerosis is a demyelinating disease that has a variable clinical course from a relapsing-remitting disease to one that is relentlessly progressive.<sup>292</sup> While an immune-mediated inflammatory process is considered central to the pathogenesis, anti-inflammatory therapies have limited effectiveness in promoting remyelination.<sup>293</sup> Insulin like growth factor I has been considered as a possible therapeutic approach to MS. Insulin like growth factor I promotes myelin production by oligodendrocytes.<sup>112,294,295</sup> Insulin like growth factor I and IGF1R are upregulated at the edges of demyelinated plaques<sup>296</sup>; however, it has been shown that oligodendrocytes within MS lesions have reduced IGF1R expression.<sup>297</sup> Mice overexpressing IGF-I are protected from cuprizone-induced demyelination,<sup>298</sup> while ablation of brain IGF1R prevents remyelination in this animal model.<sup>299</sup> However, in mice with experimental autoimmune encephalomyelitis, a transient improvement in clinical indices and remyelination in response to IGF-I, delivered using osmotic subcutaneous pumps, is lost in the chronic phase of the disease.<sup>300</sup>

In patients with MS, IGF-I concentrations in the circulation<sup>301</sup> and CSF<sup>302</sup> are no different to a control group; however, it is possible that the observed increases in IGFBP expression<sup>296,301,302</sup> or reduced oligodendrocyte IGF1R expression,<sup>297</sup> modulate IGF bioactivity. A 6-month pilot study found no impact of IGF-I on magnetic resonance imaging or clinical measures of disease activity.<sup>303</sup> In this study, IGF-I was delivered subcutaneously, and it remains to be seen whether alternative approaches that target oligodendrocyte IGF signalling pathways are effective.

### *Cerebrovascular disease*

Recent data from the Framingham study indicate that, during mean follow-up of 10.2 years, individuals in the lowest quintile of serum IGF-I concentrations have a 2.3-fold higher risk of incident ischaemic stroke<sup>304</sup>; however, it is not known whether this is a causal relationship and studies of the predictive role of IGF-I in patients who have sustained strokes are equivocal.<sup>127</sup>

In a rat model of unilateral hypoxic-ischaemic brain injury, IGF-I accumulates in the damaged hemisphere within 5 hours of severe injury, and at 3 days there is increased IGF-I production by microglia and increased IGFBP-2 expression in perineuronal reactive astrocytes throughout the hemisphere.<sup>305</sup> This was associated with reduced expression of IGFBP-3 and IGFBP-5 expression in reactive microglia and neurones in the injured hippocampus, increased expression of IGFBP-6 in choroid plexus, ependyma and reactive glia and no change in IGF1R.

In animal studies of ischaemic brain injury, there is convincing evidence of a protective effect of IGF-I on cortical neurons. In foetal lambs, IGF-I delivered into a lateral cerebral ventricle 2 hours after a hypoxic ischemic insult induced by transient carotid artery occlusion in utero reduces neuronal loss and incidence of seizures.<sup>306</sup> In rats, after unilateral hypoxic-ischaemic injury following transient middle cerebral artery occlusion, intramuscular IGF-I injection decreases neuronal apoptosis and improves motor function, effects that are eliminated by co-administration of an inhibitor of IGF1R.<sup>307</sup> Using this model of cerebral ischaemia, the benefit of physical activity on function recovery and enhanced neurogenesis is associated with increased IGF-I expression in the peri-infarct region.<sup>308</sup> IGF-I promotes receptor-mediated anchorage of endothelial cells, stabilising the microvascular cytoskeleton under these conditions.<sup>309</sup> In another model of transient focal cerebral ischaemia using endothelin-1 in conscious rats, subcutaneous IGF-I treatment reduced infarct volumes and increased motor-sensory functions.<sup>310</sup> Using the same model in hypertensive rats, infarct size was greater and IGF-I was less protective, but significantly reduced microglial activation, not seen in normotensive animals.

The N-terminal tripeptide of IGF-I is also active after unilateral hypoxic-ischaemic brain injury in rats, preventing neuronal apoptosis, promoting astrocyte survival and inhibiting microglial proliferation following intravenous infusion.<sup>311</sup> After cardiac arrest in rats, a modest neuroprotective effect of intracerebral ventricular infusion of N-terminal tripeptide was seen.<sup>312</sup> After unilateral hypoxic-ischaemic brain injury, intracerebral ventricular infusion of des(1-3)IGF-I is less potent than IGF-I in preventing neuronal loss.<sup>313</sup> It is possible that this is due to the additional effect of the N-terminal tripeptide, however co-administration of IGF-II blocked the effect of IGF-I and displacement from IGFBPs that play a targeting role was a suggested explanation. In mice exposed to cerebral hypoxic-ischaemic injury, the increased IGF-I expression

around the injury is associated with IGFBP-2 expression in activated astrocytes, with evidence that IGF-I is an paracrine/autocrine mitogen for microglia/macrophages under these conditions.<sup>314</sup> The role of IGFBPs as facilitators of brain IGF action and the role of IGF-II and IGF2R following cerebral ischaemia remain to be fully explored.

### *Traumatic nervous system injury*

Traumatic brain injury during early development is an important cause of cognitive dysfunction and is associated with epigenetic changes.<sup>315</sup> After traumatic brain injury in rat pups, hippocampal IGF-I expression is increased and associated with epigenetic modifications in the promoter region.<sup>316</sup> A decrease in circulating IGF is also predictive of cognitive dysfunction from hippocampal damage.<sup>317</sup> Increased IGF-I expression in response to traumatic injury is seen in both adult and 2 week old mice.<sup>318</sup> A penetrating cerebral wound in adult rats leads to acute and transient increases in expression of IGF-I, IGF1R and IGFBP-2 in injury-responsive astrocytes and neurones and IGFBP-3 in microvascular endothelium, with IGFBP-4 and -5 expressed in astrocytes and neurones later in the wounding response.<sup>319</sup> There appears to be a therapeutic window of at least 6 hours for central infusion of IGF-I to promote neurobehavioural recovery following traumatic brain injury in mice.<sup>320</sup>

Insulin like growth factor I and IGFBP-2 are likely to play a more general and widespread neuroprotective role in the nervous system. Increases in IGF-I and IGFBP-2 expression are seen in astrocytes following cryogenic spinal cord injury in adult rats<sup>321</sup> and in the hippocampus in response to cytotoxic damage.<sup>322</sup> IGF-I delivered subcutaneously or intracerebroventricularly partially rescues neurones and restores motor coordination in a rat model of cerebellar ataxia induced by 3-acetylpyridine.<sup>323</sup> There may be unwanted effects of IGF-I in damaged peripheral nerves. Neutralising anti-IGF-I antibodies reduced collateral axonal sprouting after peripheral nerve lesion<sup>324</sup> and an IGF1R antagonist reduced IGF-I-induced hyperalgesia in a mouse model of type 2 diabetes.<sup>325</sup>

### **IGF System As A Therapeutic Target**

There is sufficient evidence for a specific role of the IGF/insulin system for it to be worth considering as a therapeutic target in AD and other neurodegenerative diseases.<sup>326,327</sup> However, these disorders are characterised by IGF and insulin resistance, and directing therapy towards the endocrine IGF/insulin system are likely to have limited effectiveness. Systemic approaches that increase neurovascular coupling and increase transfer at the blood-brain barriers are worthy of consideration. Inhibitors of glycogen synthase kinase 3 $\beta$ , by modulation of megalin transport, increase brain IGF-I levels.<sup>328</sup> Approaches that target neuronal IGF/insulin signalling are also appealing. Gene therapy would have advantages in meeting this goal, with the attendant challenges in reaching target areas in the nervous system.<sup>329</sup> Genomic and proteomic approaches that identify

the interaction of IGF-I with other growth factor pathways that prevent apoptosis, are likely to hold promise in identifying potential drug targets.<sup>252,330,331</sup>

In addition to diseases in which the IGF system is likely to have a specific role, the more general neuroprotective effects make it worthwhile considering for a range of other disorders. However, in a series of clinical trials of patients with ALS, the use of IGF-I delivered subcutaneously has not been promising, with no improvement in survival.<sup>332,333</sup> In humans, several studies have demonstrated that GH improves neuron recovery and clinical outcome following traumatic brain injury.<sup>333</sup> In the light of studies using IGF-I in rodents, described in preceding sections, it might be that approaches that combine the use GH and IGF-I are worthwhile trying in humans. The combination of GH and IGF-I delivered intravenously for two weeks improved metabolic and nutritional endpoints in patients after acute traumatic brain injury,<sup>334</sup> however effects on neurological function were not reported.

Systemic administration of IGF-I is facilitated by approaches that prolong the half-life or promote IGF delivery. In trials of IGF-I for retinopathy of prematurity, IGF-I was delivered complexed with IGFBP-3.<sup>335</sup> Early trials with this combination, however, have failed to show a positive effect on the prevention of retinopathy of prematurity.<sup>336</sup> In a mouse model of motor neuron degeneration, IGF-I coupled with polyethylene glycol extend its circulating half-life, prolonged survival, maintained motor coordination, and rescued motor neurons from cell death.<sup>337</sup> Microsphere formulations that provided controlled release from subcutaneous depots are associated with extended survival and enhanced motor co-ordination in a mouse model of spinocerebellar neurodegeneration.<sup>338</sup> Use of an IGF-I analogue with high IGFBPs and no biological activity through IGF1R, increased availability of endogenous IGFs and had a neuroprotective effect in rat model of hypoxia-ischaemia.<sup>339</sup>

Therapeutic approaches that deliver IGFs directly to their target, or ones increasing IGF/insulin sensitivity within the nervous system deserve focus. Intranasal administration of insulin raises central nervous system levels without raising plasma levels<sup>340</sup> and early clinical trials in humans were promising.<sup>341</sup> Intranasal delivery of insulin improves some tests of memory in patients with AD without the *APOEε4* allele.<sup>342</sup> Success of these approaches raise the hypothesis that intranasal IGF-I might be an option for the treatment of depression,<sup>343–345</sup> or for improving cognitive function in normal ageing. Peripheral IGF-I infusion improves spatial reference memory and working memory in healthy ageing rats.<sup>346</sup> Studies of intracerebroventricular IGF-I gene therapy in ageing rats improves motor performance.<sup>347</sup> and modulates relevant hippocampal genes.<sup>348</sup> Intracerebroventricular FGF-2 also enhances neurogenesis in the hippocampus of aged rats.<sup>349</sup> Therapeutic approaches that combine IGF-I with other growth factors might be effective.<sup>350</sup> Since the ERK pathway is often coactivated with the PI3K/Akt signalling pathway,<sup>351</sup> the use of EGF might be considered. Insulin like growth factor I

mediates resistance to anti-EGF therapy in glioblastoma cells<sup>352</sup> and insulin and EGF have been shown to act synergistically to promote astrocyte survival and proliferation.<sup>353</sup> There are connections between sphingolipid and IGF signalling<sup>354</sup> and an effect of Klotho on IGF-I signalling<sup>355</sup> that might have implications for the management of nervous system disease.

The possibility of generating the main cell types of the nervous system from multipotent neural stem cells is an important focus for regenerative medicine<sup>329,356</sup> and the IGF system will play a key role, most likely in combination with other growth factors. Cell replacement therapy have been pursued for PD.<sup>168</sup> Human neural progenitor cells produced to release IGF-I have improved survival and, when transplanted into the substantia nigra in the 6-hydroxydopamine rat model of PD, exert trophic effects on degenerating dopamine neurons.<sup>357</sup> Combinations of IGF-I with FGF<sup>241</sup> or BDNF and glial-derived neurotrophic factor have been used to prepare neural progenitor cells for transplantation.<sup>184</sup>

## Conclusions and Recommendations

IGF system components are widely expressed in the nervous system where there is substantial evidence for neuroprotective and neurotrophic actions of IGF-I. Low IGF-I is associated with longevity and this apparent paradox is best understood when the complexity of the IGF system is taken into account. Association of IGF with IGFBP-2 and IGFBP-5 in the nervous system may promote local IGF action, while high concentrations or the presence of other IGFBPs may be inhibitory. Nutrition and insulin which are important regulators of IGF-I production, have other effects on the nervous system, through pathways that interact with the IGF1R. It is important to note that much of our understanding of the IGFs in the nervous comes from experimental studies in rodents where there are differences in neurogenesis compared to humans,<sup>33,93</sup> with a focus on IGF-I and not IGF-II. Since the IRA isoform is expressed at significant concentrations in brain tissue,<sup>6</sup> IRA/IGF1R hybrids are also present and IGF-II may therefore have a distinct role. These gaps in knowledge should be addressed in future research. In particular (a) the role of brain IGFBPs as regulators of local IGF actions, and what are their IGF-independent roles; (b) the role of IGF-II and, in particular is there a potential therapeutic role in human neurodegenerative disease? and (c) the effect of a combination approach to therapy; using other growth factors with IGF-I or IGF-II across the spectrum of nervous system disorders.

## Author Contributions

ML and GB developed the structure and arguments for the paper, wrote and critically revised, and approved the final version.

## Disclosure and Ethics

The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. There

are no conflicts of interest to declare. The authors also confirm that this article is unique and not under consideration or published in any other publication, and no copyrighted material is reproduced.

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